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Vaccination with Dendritic Cell Myeloma Fusions in Conjunction with Stem Cell Transplantation and PD-1 Blockade

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14. ABSTRACT

Most patients with multiple myeloma achieve a complete or near complete response following autologous transplantation. However, patients experience disease relapse from a persistent reservoir of chemotherapy resistant disease. There has been strong interest in developing immunotherapeutic strategies to eradicate residual disease following autologous transplantation. Our group has developed a tumor vaccine model whereby dendritic cells are fused with tumor cells. In clinical trials, vaccination with fusion cell results in anti-tumor immune and disease responses in a subset of patients. However, vaccine efficacy is blunted by tumor mediated immune suppression and the increased presence of regulatory T cells characteristic of patients with malignancy. An important element contributing to tumor mediated immune suppression is the PD-1/PDL-1 pathway. PD-L1 exerts a significant role in promoting T cell tolerance by binding PD-1 on activated T cells and suppressing their capacity to secrete stimulatory cytokines. We have demonstrated that blockade of this pathway results in enhanced immune responses to DC/myeloma fusion cells ex vivo. In the proposed study, we will examine toxicity, immunologic effect and clinical efficacy of CT-011 therapy following stem cell transplantation for patients with myeloma. These endpoints will then be assessed in patients undergoing combined therapy with the vaccine and antibody.

15. SUBJECT TERMS
DC/myeloma fusion vaccine, PD1 blockade, immunotherapy, multiple myeloma

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A. INTRODUCTION

In this project, we are conducting a clinical trial in which patients with multiple myeloma are treated with an anti-PD1 antibody (CT-011) alone (Cohort 1) and in conjunction with a dendritic cell/myeloma fusion cell vaccine (Cohort 2) following autologous transplantation. The goal of the project is determine the effect of CT-011 alone, and in conjunction with a DC/myeloma fusion cell vaccine, to stimulate effective anti-tumor immunity and disease response.

B. BODY

Clinical Trial

The clinical study is being conducted in two stages. In the first stage, a pilot study is being conducted in which patients are treated with CT-011 alone following autologous transplant. The primary objective of this stage is to explore immunologic responses to CT-011 in the post-transplant period. The secondary objective is to assess the toxicity of treating patients with CT-011 in the post-transplant setting.

In the second stage, patients receive a combination of CT-011 and DC/myeloma fusion vaccination. The primary objective is to determine if cellular immunity is induced by treatment with monoclonal antibody CT-011 and DC/myeloma fusion cells in conjunction with stem cell transplant. The secondary objectives of this stage are: 1) To assess the toxicity associated with treating multiple myeloma patients with monoclonal antibody CT-O11 in combination with DC/myeloma fusion vaccine following autologous transplant, 2) To correlate levels of circulating activated and regulatory T cells with immunologic response, and 3) To define anti-tumor effects using serum markers, radiological studies, and time to disease progression.

The targeted study population includes patients with multiple myeloma who are potential candidates for high dose chemotherapy with stem cell rescue. In cohort 1, participants receive three infusions of CT-011 at doses of doses of 3mg/kg given at 6 week intervals beginning 1-3 months following autologous transplant. In cohort 2, participants receive three infusions of CT-

011 given at six week intervals, in conjunction with vaccination with DC/myeloma fusion cells. Vaccination is given one week before each infusion of CT-011 and is given in conjunction with GM-CSF on the day of vaccination and for three days thereafter.

Status: The protocol (DF-HCC protocol number 09-061) is open to accrual at the DF/HCC as of March 19, 2010. Rambam Medical Center (RMC) in Haifa, Israel was added on April 26, 2011. Chaim Sheba Medical Center (CHSH) in Tel Hashomer, Israel was added on January 14, 2014. As of May 1, 2014, 64 patients have been screened. There have been eight screen failures: five patients did not meet eligibility criteria and three patients elected to pursue only standard of care therapy. To date, 58 participants have met eligibility criteria and have been enrolled: 27 patients on the first cohort (19 at DF/HCC and 8 at RMC) and 31 patients on the second cohort (25 at DF/HCC,4 at RMC, and 2 at CHSH.)

Cohort 1: At DF/HCC, 10 participants were removed from study prior to initiating study treatment: six participants came off-study to pursue only standard of care therapy, one participant progressed during induction chemotherapy, and one participant was not moving forward with transplant. In addition, two participants died during standard of care induction chemotherapy, before initiating study treatment. One participant died on 11/5/10 after suffering a cardiac arrest in his home; the event was reported to the Dana Farber Harvard Cancer Center IRB on 11/11/10. Another participant committed suicide on 1/19/12; the event was reported to the Dana Farber Harvard Cancer Center IRB on 1/20/12. At RMC, two participants were removed from study prior to initiating study treatment to pursue only standard of care therapy. At RMC, two participants were removed from study prior to initiating study treatment to pursue SOC therapy only.

Cohort 2: Four participants have come off-study (2 at DF/HCC and 2 at RMC). prior to initiating study treatment to pursue SOC treatment only.

All participants enrolled onto the first cohort at both DF/HCC and RMC have completed treatment and active follow-up and are now in long-term follow-up.

Of the subjects enrolled onto the second cohort at DF/HCC, six have completed treatment and active follow-up and are now in long-term follow-up, two have completed treatment and are now in active follow-up, six are currently receiving treatment, five have undergone tumor collection and dendritic cell collection for vaccine generation and are completing pre-transplant chemotherapy; and three have undergone tumor collection and cryopreservation but have not yet undergone dendritic cell collection. Of the subjects enrolled onto the second cohort at RMC and CHSH, all four subjects are completing standard of care induction chemotherapy prior to transplant.

The continuing review approval notice from the DF/HCC IRB for this study can be found in Appendix P.

Subject Study Information

Table 1: Screen Failures

Subject Initials	Screening Number	Consent Date	Age	Gender	Race/ Ethnicity	Reason
ES	2	5/25/10	54	F	White	Failure to meet eligibility criteria
JP	5	7/16/10	51	M	Hispanic	Failure to meet eligibility criteria
GW	7	10/28/10	59	M	White	Failure to meet eligibility criteria
JD	13	5/3/2011	51	M	White	Failure to meet eligibility criteria
EB	18	7/25/11	62	F	African American	Elected to pursue standard of care therapy only
JH	19	8/15/11	72	F	White	Elected to pursue standard of care therapy only
JR	30	12/6/11	61	M	Hispanic	Failure to meet eligibility criteria
DA	45	1/10/13	59	M	White	Failure to meet eligibility criteria

Table 2: Subjects Enrolled

Subject Initials	Site	Screening Number	Enrollment Number	Consent Date	Registration Date	Age	Gender	Race/ Ethnicity	Off -Study Date	Reason Off-Study
LC	DF/HCC	1	1	5/10/2010	5/13/2010	48	M	White	8/14/2010	Disease Progression
RG	DF/HCC	3	2	6/23/2010	7/2/2010	70	M	White	11/5/2010	Death
RP	DF/HCC	4	3	7/1/2010	7/9/2010	52	F	Black	N/A	N/A
CC	DF/HCC	6	4	9/16/2010	9/29/2010	55	M	White	12/12/2011	Disease Progression
KF	DF/HCC	8	5	12/21/2010	12/30/2010	55	F	White	8/6/2013	Disease Progression
DW	DF/HCC	9	6	12/27/2010	1/7/2011	47	M	White	10/12/2011	Elected to pursue SOC therapy
DF	DF/HCC	10	7	12/29/2010	1/13/2011	63	M	White	7/11/2013	Disease Progression
GF	DF/HCC	11	8	1/3/2011	1/28/2011	73	F	White	10/19/2011	Elected to pursue SOC therapy
SM	DF/HCC	12	9	2/4/2011	2/15/2011	58	M	White	N/A	N/A
RR	DF/HCC	14	10	5/16/2011	5/18/2011	67	M	White	N/A	N/A
AG	DF/HCC	15	11	5/26/2011	6/6/2011	45	F	White	9/25/2012	Elected to pursue SOC therapy
KI	RMC	16	12	6/9/2011	6/14/2011	61	M	White	11/6/2011	Elected to pursue SOC therapy
BF	RMC	17	13	7/19/2011	7/21/2011	64	F	White	1/14/2013	Disease Progression
RB	DF/HCC	20	14	8/22/2011	8/26/2011	58	M	White	3/1/2012	Elected to pursue SOC therapy
SMM	RMC	21	15	9/5/2011	9/12/2011	55	M	White	9/16/2013	Disease Progression
FM	DF/HCC	22	16	10/12/2011	10/26/2011	50	M	Hispanic	4/24/2014	Disease Progression
ES	DF/HCC	23	17	11/3/2011	11/10/2011	55	F	White	6/21/2012	N/A
KM	DF/HCC	24	18	10/21/2011	11/10/2011	49	M	Black	1/19/2012	Death
KM	DF/HCC	25	19	11/17/2011	11/21/2011	56	F	White	3/15/2013	Disease Progression
KR	RMC	26	20	11/22/2011	11/30/2011	47	M	White	11/25/2012	Disease Progression
NP	DF/HCC	27	21	12/16/2011	12/21/2011	62	F	White	8/10/2012	Elected to pursue SOC therapy
TR	RMC	28	22	1/5/2012	1/9/2012	66	F	White	5/8/2013	Disease Progression
BB	DF/HCC	29	23	1/20/2012	1/30/2012	60	M	White	N/A	N/A
TB	RMC	32	24	2/2/2012	2/3/2012	60	M	White	N/A	N/A
IC	DF/HCC	31	25	1/5/12	2/17/12	66	F	Hispanic	11/26/2012	Elected to pursue SOC therapy
LY	RMC	33	26	5/4/2012	5/8/2012	64	M	White	N/A	N/A
HH	RMC	34	27	6/19/2012	6/21/2012	30	M	White	11/27/2012	Elected to pursue SOC therapy
CG	DF/HCC	35	28	7/17/2012	7/23/2012	61	F	White	N/A	N/A
SF	DF/HCC	36	29	8/3/2012	8/7/2012	47	M	White	N/A	N/A

Subject Initials	Site	Screening Number	Enrollment Number	Consent Date	Registration Date	Age	Gender	Race/ Ethnicity	Off -Study Date	Reason Off-Study
PLL	DF/HCC	37	30	10/11/2012	10/18/2012	66	M	White	3/21/2013	Not receiving transplant
FH	DF/HCC	38	31	10/11/2012	11/1/2012	66	M	White	N/A	N/A
WP	DF/HCC	39	32	11/26/2012	12/11/2012	63	M	White	N/A	N/A
EH	DF/HCC	40	33	11/27/2012	12/13/2012	68	F	White	N/A	N/A
AW	DF/HCC	41	34	12/13/2012	12/17/2012	53	F	White	N/A	N/A
MS	DF/HCC	42	35	12/18/2012	12/21/2012	68	M	White	N/A	N/A
JG	DF/HCC	43	36	11/28/2012	1/4/2013	70	F	White	9/9/2013	Elected to pursue SOC therapy
HB	DF/HCC	44	37	2/4/2013	2/7/2013	75	M	White	N/A	N/A
SA	RMC	46	39	2/3/2013	2/7/2013	47	F	White	N/A	N/A
MAG	DF/HCC	47	38	2/5/2013	2/12/2013	66	F	White	N/A	N/A
DP	DF/HCC	48	40	3/1/2013	3/7/2013	71	F	White	N/A	N/A
DH	DF/HCC	49	41	3/6/2013	3/21/2013	59	M	White	N/A	N/A
SS	RMC	50	42	3/21/2013	3/25/2013	69	M	White	9/16/2013	Elected to pursue SOC therapy
CK	DF/HCC	51	43	4/17/2013	4/26/2013	49	F	White	N/A	N/A
JS	DF/HCC	52	44	5/7/2013	5/9/2013	62	F	White	N/A	N/A
MB	DF/HCC	53	45	5/10/2013	5/20/2013	52	M	White	N/A	N/A
JC	DF/HCC	54	46	4/26/2013	5/31/2013	71	M	Black	10/05/2013	Ineligible for transplant
BT	DF/HCC	55	47	6/18/2013	6/21/2013	61	M	White	N/A	N/A
DD	DF/HCC	56	48	9/17/2013	9/19/2013	65	M	White	N/A	N/A
JR	DF/HCC	57	49	11/21/2013	11/25/2013	75	M	Black	N/A	N/A
PE	DF/HCC	58	50	11/25/2013	12/2/2013	66	M	Hispanic	N/A	N/A
EZ	RMC	59	51	1/20/2014	1/20/2014	57	M	White	N/A	N/A
JZ	DF/HCC	60	52	1/27/2014	1/30/2014	48	M	White	N/A	N/A
AT	RMC	61	53	2/11/2014	2/15/2014	48	M	White	N/A	N/A
TH	DF/HCC	62	54	2/19/2014	2/24/2014	42	M	White	N/A	N/A
DZ	CHSH	63	55	2/24/2014	2/26/2014	49	M	Whire	N/A	N/A
RE	CHSH	64	56	2/25/2014	3/7/2014	51	F	Whire	N/A	N/A
EP	DF/HCC	65	57	4/3/2014	4/8/2014	57	F	White	N/A	N/A
RL	DF/HCC	66	58	4/22/2014	4/29/2014	66	M	White	N/A	N/A

TABLE 3: PARTICIPANTS WHO HAVE RECEIVED TREATMENT

SUBJECT ID	Cohort and Dose Administered	Treatment Dates	Clinical Outcome
RP/PM3 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 2/14/11 #2. 3/28/11 #3. 5/9/11	Best response at the end of transplant was complete response. Since completing treatment, the participant has remained in a complete response.
CC/PM4 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 5/4/11 #2. 6/15/11 #3. 7/27/11	Best response at the end of transplant was complete response. The participant developed disease progression five months following last treatment.
KF/PM5 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1 6/28/11 #2. 8/9/11 #3. 9/20/11	Best response at the end of transplant was complete response. The participant developed disease progression 23 months following last treatment.
DF/PM7 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 3/6/12 #2. 4/26/12 #3. 6/7/12	Best response at the end of transplant was very good partial response. The participant developed disease progression 12 months following last treatment.
SM/PM9 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 9/19/11 #2. 10/31/11 #3. 12/12/11	Best response at the end of transplant was very good partial response. Since completing treatment, the participant has remained stable at his best response.
RR/PM10 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 1/31/12 #2. 3/13/12 #3. 4/24/12	Best response at the end of transplant was complete response. Since completing treatment the participant has remained in a complete response.
BF/PM13 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 1/19/11 #2. 3/1/12 #3. 4/11/12	Best response at the end of transplant was very good partial response. The participant developed disease progression 13 months following last treatment.
SMM/PM15 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 4/5/12 #2. 5/15/12 #3. 6/28/12	Best response at the end of transplant was very good partial response. The participant developed disease progression 15 months following last treatment.
FM/PM16 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 5/24/12 #2. 7/5/12 #3. 8/16/12	Best response at the end of transplant was very good partial response. The participant developed disease progression at 22 months following last treatment.
KM/PM19 (DF/HCC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 5/21/12 #2. 7/2/12 #3. 8/13/12	Best response at the end of transplant was a partial response. The participant developed disease progression 7 months following last treatment.
KR/PM20 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 5/30/12 #2. 7/12/12 #3. 8/22/12	Best response at the end of transplant was very good partial response. The participant developed progressive disease four months following completion of study treatment and was removed from study.
TR/PM22 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 8/23/12 #2. 9/27/12 #3. 11/7/12	Best response at the end of transplant was complete response. The participant developed disease progression at 6 months following last treatment.

SUBJECT ID	Cohort and Dose Administered	Treatment Dates	Clinical Outcome
BB/PM23 (DF/HCC)	Cohort 2: CT-011 Alone 3 doses at 3mg/kg	#1. 7/17/13 #2. 10/9/13 #3. 11/20/13	Best response at the end of transplant was a very good partial response. Since completing treatment, the participant has remained in a VGPR.
TB/PM24 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 7/18/12 #2. 9/6/12 #3. 10/11/12	Best response at the end of transplant was a very good partial response. Since completing treatment, the participant has remained in a VGPR.
LY/PM26 (RMC)	Cohort 1: CT-011 Alone 3 doses at 3mg/kg	#1. 12/6/12 #2. 1/17/13 #3. 3/4/13	Best response at the end of transplant was very good partial response. Since completing treatment the participant has remained in a VGPR.
CG/PM28 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 5/9/13 Inf #1. 5/16/13 Vac #2. 6/20/13 Inf #2. 6/27/13 Vac #3. 8/8/13 Inf #3. 8/15/13	Best response at the end of transplant was a near complete response. Since completing treatment, the participant has remained in a near complete response.
SF/PM29 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 3/7/13 Inf #1. 3/14/13 Vac #2. 4/18/13 Inf #2. 4/25/13 Vac #3. 5/30/13 Inf #3. 8/15/13	Best response at the end of transplant was complete response. Since completing treatment, the participant has remained in a complete response.
WP/PM32 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 7/29/13 Inf #1. 8/5/13 Vac #2. 9/9/13 Inf #2. 9/16/13 Vac #3.10/21/13 Inf #3. 10/28/13	Best response at the end of transplant was a very good partial response. Since completing treatment, the participant has remained in a very good partial response
EH/PM33 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 6/4/13 Inf #1. 6/11/13 Vac #2. 7/16/13 Inf #2. 7/23/13 Vac #3. 8/27/13 Inf #3. 9/3/13	Best response at the end of transplant was complete response. Since completing treatment, the participant has remained in a complete response.
AW/PM34 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 7/16/13 Inf #1. 7/23/13 Vac #2. 9/3/13 Inf #2. 9/10/13 Vac #3 10/15/13 Inf #3. 10/22/13	Best response at the end of transplant was a complete response. Since completing treatment, the participant has remained in a complete response.
MS/PM34 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 8/6/13 Inf #1. 8/13/13 Vac #2. 9/17/13 Inf #2. 9/24/13	Best response at the end of transplant was a partial response. Since completing treatment, the participant has remained in a partial response.
AS/PM37 (RMC)	Cohort 2: CT-011 3 doses at 3mg/kg (did not generate enough cells for vaccine)	Inf #1. 9/9/13 Inf #2. 10/20/13 Inf #3. 12/8/13	Best response at the end of transplant was CR. Since completing treatment the participant has remained in complete response.

SUBJECT ID	Cohort and Dose Administered	Treatment Dates	Clinical Outcome
HB/PM38 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 9/24/13 Inf #1. 10/1/13 Vac #2. 1/30/14 Inf #2. 2/13/14 Vac #3 3/20/14 Inf #3. 3/27/14	Best response at the end of transplant was a very good partial response. Since completing treatment the participant has remained in a very good partial response.
MAG/PM39 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1. 9/24/13 Inf #1. 10/1/13 Vac #2. 11/5/13 Inf #2. 11/12/13 Vac #3 12/17/13 Inf #3. 12/26/13	Best response at the end of transplant was a very good partial response. Since completing treatment the participant has remained in a very good partial response.
DP/PM40 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac#1 11-21-13 Inf #1 11-29-13 Vac #2 1-9-14 Inf #2 1-16-14 Vac #3 2-19-14 Inf #3 2-27-14	Best response at the end of transplant was a near complete response. Since completing treatment the participant has remained in a near complete response.
DH/PM41 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1 4-3-14 Inf # 1 4-9-14 Vac #2 PND Inf #2 PND Vac #3 PND Inf #3 PND	Best response at the end of transplant was a very good partial response. The participant will have his disease reassessed at one month following completion of treatment.
CK/PM43 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1 2-11-14 Inf #1 3-7-14 Vac #2 4-8-14 Inf #2 4-16-14 Vac #3 PND Inf #3 PND	Best response at the end of transplant was a partial response. The participant will have her disease reassessed at one month following completion of treatment.
JS/PM44 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Inf #1 1-6-14 Inf #2 2-26-14 Inf # 3 4-7-14	Best response at the end of transplant was a very good partial response. Since completing treatment the participant has remained in a very good partial response.
MB/PM45 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1 2-11-14 Inf #1 2-27-14 Vac #2 4-1-14 Inf #2 4-10-14 Vac #3 PND Inf #3 PND	Best response at the end of transplant was a complete response. The participant will have his disease reassessed at one month following completion of treatment.
BT/PM47 (DF/HCC)	Cohort 2: DC/MM Fusion Vaccine 3 doses at 5x10^6 cells + CT-011 3 doses at 3mg/kg	Vac #1 2-14-14 Inf #1 2-20-14 Vac #2 4-1-14 Inf #2 4-8-14 Vac #3 PND Inf #3 PND	Best response at the end of transplant was a very good partial response. The participant will have his disease reassessed at one month following completion of treatment.

Immunological Responses to Date: Immunologic response was determined by quantifying circulating tumor reactive T cells at each time point as defined by the percent T cells expressing IFNg in response to ex vivo exposure to autologous tumor lysate. Results are presented as the percentage of CD4 or CD8 T cells expressing IFNg.

Pt #	IFNg (REN)	Pre-Mobilization	Pre-Infusion #1	Pre-Infusion #2	Pre-Infusion #3	Post 1 month	Post 3 month	Post 6 month
PM03	CD4/IFNg	0.21	0.39	1.23	3.27	1	1.85	3.42
	CD8/IFNg	0.42	3.43	11.33	13.3	3.34	4.61	9.22
PM04	CD4/IFNg	0.27	0.14	4.79	2.82	11	5.97	off study
	CD8/IFNg	2.56	1.4	3.32	3.9	10.7	3.37	off study
PM05	CD4/IFNg	0.07	0.33	0.39	4.08	3.82	0.19	0.31
	CD8/IFNg	0.49	0.39	1.25	11.99	11.76	1.4	0.49
PM09	CD4/IFNg	0.55	5.2	1.27	2.53	1.2	0.67	0.35
	CD8/IFNg	0.7	2.6	10.63	6.68	7.31	5.1	3.61
PM10	CD4/IFNg	0.23	0.20	0.50	0.17	0.42	0.56	0.52
	CD8/IFNg	2.30	3.20	5.47	0.71	4.20	3.69	4.32
PM16	CD4/IFNg	0.53	0	1.71	nd	0	0.2	0
	CD8/IFNg	nd	nd	0.69	nd	nd	0.27	0.5
PM19	CD4/IFNg	0.14	3.96	nd	nd	nd	1.97	1.67
	CD8/IFNg	0	nd	nd	nd	nd	2.99	1.13

0.39 1.25

TREATMENT RELATED ADVERSE EVENTS

Subject ID	AE	Start Date	CTC Grade	Relationship to CT-011	Relationship toVaccine	Action Taken Regarding TX	Outcome
PM03	Leukopenia	3/14/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM03	Leukopenia	5/2/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM03	Leukopenia	5/23/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM03	Leukopenia	7/11/11	2	POSSIBLE	N/A	NONE	RESOLVED
PM03	Leukopenia	7/13/11	1	POSSIBLE	N/A	NONE	ONGOING
PM03	ANC	5/9/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM03	ANC	5/23/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM03	ANC	6/10/11	2	POSSIBLE	N/A	NONE	RESOLVED
PM03	ANC	7/11/11	3*	POSSIBLE	N/A	NONE	RESOLVED
PM03	ANC	7/13/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM03	ANC	9/2/11	2	POSSIBLE	N/A	NONE	RESOLVED
PM03	ANC	9/30/11	1	POSSIBLE	N/A	NONE	ONGOING

Subject ID	AE	Start Date	CTC Grade	Relationship to CT-011	Relationship toVaccine	Action Taken Regarding TX	Outcome
PM03	Allergic Rhinitis	7/11/11	1	POSSIBLE	N/A	NONE	ONGOING
PM04	Diarrhea	5/5/11	1	PROBABLE	N/A	NONE	RESOLVED
PM04	Diarrhea	7/27/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM04	Diarrhea	9/5/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM04	Pain, Joint	8/27/11	2	POSSIBLE	N/A	NONE	RESOLVED
PM04	Night Sweats	9/3/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM04	Fatigue	8/27/11	2	POSSIBLE	N/A	NONE	RESOLVED
PM04	Fatigue	9/18/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM05	Diarrhea	7/7/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM05	Diarrhea	7/31/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM05	Diarrhea	9/27/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM05	Diarrhea	10/19/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM07	diarrhea	3/6/12	1	POSSIBLE	N/A	NONE	RESOLVED
PM09	Diarrhea	10/10/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM09	Rash	10/1/11	2	POSSIBLE	N/A	NONE	ONGOING
PM09	Thyroid Function, Low	10/31/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM09	Eosinophils, Elevated	12/12/11	1	POSSIBLE	N/A	NONE	RESOLVED
PM10	Diarrhea	2/2/12	1	PROBABLY	N/A	NONE	RESOLVED
PM10	Diarrhea	2/13/12	1	POSSIBLE	N/A	NONE	RESOLVED
PM10	Diarrhea	2/23/12	1	PROBABLY	N/A	NONE	RESOLVED
PM10	Diarrhea	4/27/12	1	PROBABLY	N/A	NONE	RESOLVED
PM10	Nausea	2/1/12	1	PROBABLY	N/A	NONE	RESOLVED
PM10	Thyroid Function, Low	3/13/12	1	POSSIBLE	N/A	NONE	RESOLVED
PM15	Weakness	4/5/12	1	POSSIBLE	N/A	NONE	RESOLVED
PM15	Periorbital Swelling	4/5/12	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Leukopenia	6/4/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Leukopenia	7/2/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Leukopenia	7/23/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Leukopenia	9/4/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Diarrhea	7/15/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Diarrhea (intermittent)	8/14/2012	2	POSSIBLE	N/A	NONE	RESOLVED
PM19	Diarrhea (intermittent)	11/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Lymphopenia	7/23/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM19	Arthralgia, hands	11/2012	1	POSSIBLE	N/A	NONE	RESOLVED
PM26	Decrease in PLT count	1/17/13	1	POSSIBLE	N/A	NONE	RESOLVED
PM29	Myalgias	3/7/2013	1	UNRELATED	POSSIBLE	NONE	RESOLVED

Subject ID	AE	Start Date	CTC Grade	Relationship to CT-011	Relationship toVaccine	Action Taken Regarding TX	Outcome
PM29	Arthralgia, R ankle	3/11/2013	1	UNRELATED	POSSIBLE	NONE	RESOLVED
PM29	Vaccine Site Reaction	3/11/2013	1	UNRELATED	DEFINITELY	NONE	RESOLVED
PM29	Ecchymosis, vaccine site	3/13/2013	1	UNRELATED	DEFINITELY	NONE	RESOLVED
PM29	Facial Flushing	3/10/2013	1	UNRELATED	POSSIBLE	NONE	RESOLVED
PM29	ANC	3/14/2013	1	UNRELATED	POSSIBLE	NONE	RESOLVED
PM29	Leukopenia	3/14/2013	1	UNRELATED	POSSIBLE	NONE	RESOLVED
PM29	Flu-like Symptoms	3/14/2013	1	POSSIBLE	UNRELATED	NONE	RESOLVED
PM29	Leukopenia	4/4/2013	1	POSSIBLE	UNRELATED	NONE	RESOLVED
PM29	ANC	4/4/2013	1	POSSIBLE	UNRELATED	NONE	RESOLVED
PM32	Musculoskeletal, other (a brief episode of muscle spasms)	7/29/2013	1	UNRELATED	PROBABLE	NONE	RESOLVED
PM32	Injection site reaction	7/29/2013	1	UNRELATED	DEFINITE (GM-CSF)	IBUPROFEN	RESOLVED
PM32	Pain, joint	8/5/2013	1	DEFINITE	DEFINITE	NONE	RESOLVED
PM32	Pain, muscle	8/5/2013	1	DEFINITE	DEFINITE	NONE	RESOLVED
PM32	Pain, muscle	9/13/2013	1	UNRELATED	DEFINITE (GM-CSF)	NONE	RESOLVED
PM32	Pain, joint	9/13/2013	1	UNRELATED	DEFINITE (GM-CSF)	NONE	RESOLVED
PM32	Injection site reaction	9/14/2013	1	UNRELATED	DEFINITE (GM-CSF)	NONE	RESOLVED
PM32	Pain, Joint	9/19/2013	1	PROBABLE	PROBABLE	NONE	RESOLVED
PM32	Rhinitis	10/23/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM32	Diarrhea	10/23/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM32	Injection site reaction	10/23/2013	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM32	Rash, chest/abd	10/28/2013	1	UNRELATED	POSSIBLY	NONE	RESOLVED
PM32	Rash, chest/abd	11/19/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM32	Pain, muscle	9/19/2013	1	PROBABLE	PROBABLE	NONE	RESOLVED
PM33	Elevated TSH	11/26/2013	1	POSSIBLY	POSSIBLY	NONE	CONT
PM34	Injection site reaction	10/17/2013	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM34	Injection site reaction	9/5/2013	1	UNRELATED	DEFINITE (GM-CSF)	NONE	RESOLVED
PM35	Neutropenia	10/8/2013	3	PROBABLE	PROBABLE	NONE	RESOLVED
PM35	Neutropenia	10/11/2013	4	PROBABLE	PROBABLE	NONE	RESOLVED
PM35	Neutropenia	10/15/2013	3	PROBABLE	PROBABLE	NONE	RESOLVED
PM35	Pain at injection site	8/6/2013	1	UNRELATED	DEFINITE (GM-CSF)	NONE	RESOLVED
PM35	Injection site reaction	9/21/2013	1	UNRELATED	DEFINITE (GM-CSF)	NONE	RESOLVED
PM37	Chills (during infusion)	12/26/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM37	Injection site reaction	1/31/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM37	Injection site reaction	2/9/2014	1	UNRELATED	PROBABLE	NONE	RESOLVED

Subject ID	AE	Start Date	CTC Grade	Relationship to CT-011	Relationship toVaccine	Action Taken Regarding TX	Outcome
PM37	Injection site reaction	3/20/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM37	Thyroid Function, Low	3/20/2014	1	POSSIBLY	POSSIBLY	NONE	ONGOING
PM39	Injection site reaction	9/25/2013	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM39	Diarrhea, Interim	10/2/2013	1	POSSIBLY	POSSIBLY	NONE	ONGOING
PM39	Pain, abd NOS, interim	10/2/2013	1	POSSIBLY	POSSIBLY	NONE	ONGOING
PM39	Pain, back, interm	10/2/2013	1	POSSIBLY	POSSIBLY	NONE	ONGOING
PM39	Leukocytes	10/15/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Pain shoulders	10/1/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Diarrhea	10/28/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Nausea	10/29/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Arthralgia	10/1/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Diarrhea	11/8/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Diarrhea	12/3/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Injection site reaction	11/6/2013	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM39	Rash, upper chest	11/9/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM39	Rash arm	11/9/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM39	Leukocytes	11/12/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM39	Nausea	11/13/2013	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM39	Pain, back	12/23/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM39	Pain, shoulder	12/23/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM39	Diarrhea	12/18/2013	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM39	Injection site reaction	12/18/2013	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM39	Pain back	1/21/2014	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM40	Injection site reaction	11/24/2013	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM40	Pain, b/l thigh	12/1/2013	1	POSSIBLY	POSS R/T CT011	NONE	RESOLVED
PM40	Diarrhea	1/12/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM40	Abdominal pain	1/14/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM40	Nausea	1/13/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM40	Anorexia	1/12/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM40	Injection site reaction	1/13/2014	1	UNRELATED	POSSIBLY	NONE	RESOLVED
PM40	Injection site reaction	2/20/2014	1	UNRELATED	POSSIBLY	NONE	RESOLVED
PM40	Diarrhea	3/2/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM40	Injection site reaction	3/3/2014	1	UNRELATED	POSSIBLY	NONE	RESOLVED
PM40	Rash	3/unk/14	1	POSSIBLY	POSSIBLY	NONE	CONT
PM41	Rash (face and scalp)	4/27/2014	2	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM41	Rash (face and scalp)	5/8/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED

Subject ID	AE	Start Date	CTC Grade	Relationship to CT-011	Relationship toVaccine	Action Taken Regarding TX	Outcome
PM41	Rash (face and scalp)	5/11/2014	2	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM41	Injection site reaction	6/4/2014	1	UNRELATED	POSSIBLY	NONE	ONGOING
PM43	Diarrhea	2/13/2014	2	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM43	Fatigue	3/8/2014	2	DEFINITE	UNRELATED	NONE	RESOLVED
PM43	ALT	5/21/2014	1	POSSIBLY	POSSIBLY	NONE	ONGOING
PM43	AST	5/21/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM43	Fatigue	4/16/2014	1	PROBABLE	UNRELATED	NONE	RESOLVED
PM44	Arthralgia	3/1/2014	1	POSSIBLY	POSSIBLY	NONE	RESOLVED
PM45	Injection site reaction	2/11/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM45	Injection site reaction	4/2/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM45	Injection site reaction	5/14/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM45	Injection site reaction	5/17/2014	2	UNRELATED	DEFINITE	NONE	RESOLVED
PM45	Injection site reaction	5/19/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM45	Headache	5/14/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM47	Injection site reaction	5/15/2014	1	UNRELATED	DEFINITE	NONE	RESOLVED
PM47	Fatigue	5/21/2014	1	POSSIBLY	UNRELATED	NONE	RESOLVED
PM47	Diarrhea	5/21/2014	1	PROBABLE	UNRELATED	NONE	RESOLVED

*The episode of grade 3 low ANC resolved to grade 1 after two days without growth factor support. This event did not meet TLT criteria.

Treatment Related Serious Adverse Events:

There has been one serious adverse events related to study treatment. On 10/11/13,participant PM35 presented to clinic for week 2 follow-up after his second infusion of CT-011 with grade 4 neutropenia (expected, probably related to CT-011 and vaccine.) The participant received neupogen per protocol. The participant returned again on 10/22/13, at which time his ANC had resolved to normal. The participant remained asymptotic and without infection. Per protocol, the participant was taken off treatment. This met the criteria for a DLT. Unrelated AEs and SAEs are listed in the summary of unrelated adverse events (see Appendix E).

Treatment Summary of Subjects that Died While on Study:

There have been two unrelated deaths on study. The participants had not initiated study treatment. One participant died on 11/5/10 after suffering a cardiac arrest in his home; the event was reported to the Dana Farber Harvard Cancer Center IRB on 11/11/10. Another participant committed suicide on 1/19/12; the event was reported to the Dana Farber Harvard Cancer Center IRB on 1/20/12. Although the unrelated deaths did not meet reporting criteria to the FDA, both were nevertheless communicated to the FDA as the events were representative of deaths on study (FDA1571: S268 sent on 11/15/10, and FDA1571: S295 sent on 1/20/12,). At RMC, one participant came off study prior to initiating study treatment to pursue only standard of care therapy.

C. REPORTABLE OUTCOMES

There are no updated reportable outcomes since last year.

D. CONCLUSIONS

The clinical trial (DF-HCC protocol 09-061) is open to accrual at both the Dana Farber Harvard Cancer Center (Boston), and Rambam Medical Center (Haifa, Israel). In total, 17 participants have initiated treatment with CT-011 alone (15 on cohort one and 2 who were enrolled to cohort 2 but did not receive vaccine) and are evaluable for response. Of these 17 participants, 8 remain without disease progression: three participants have achieved a CR and five participants have achieved a VGPR. In addition, 9 participants developed progressive disease and were subsequently removed from study. The median time without disease progression for the 17 evaluable participants is 20 months from transplant. CT-011 has been well tolerated, with possibly related adverse events consisting of transient grade 1-2 leukopenia, diarrhea, fatigue, arthralgia, rash, and peri-orbital edema. One patient developed grade 3 neutropenia, which resolved after two days without growth factor. Immunologic response was determined by quantifying circulating tumor reactive T cells prior to each dose of CT-011 and at 1, 3, 6 months following the last infusion, as defined by the percentage of T cells expressing IFNg in response to ex vivo exposure to autologous tumor lysate.

In total, 12 participants on the second cohort have received treatment with at least two doses of both DC/myeloma fusion vaccine and CT-011 and are evaluable for response. Of these 12 participants, 9 have completed their one-month follow-up. Of these 9 participants, all are without disease progression: three have achieved a complete response, two have achieved a near complete response, two have achieved a very good partial response, and one has achieved a partial response. The other four participants are still receiving treatment and will undergo disease assessment one month following completion of treatment. We are currently enrolling to the second cohort in which patients receive CT-011 in addition to the DC/MM fusion vaccine. Clinical and immunological response to the study treatment is ongoing.